

Evaluation Of The Use Of Daptomycin In Diabetic Foot Infections With Osteomyelitis

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Citation

R Stienecker, R Wolcott, M Crompton, E Hershberger, M Yoon, H Hoffman-Roberts. *Evaluation Of The Use Of Daptomycin In Diabetic Foot Infections With Osteomyelitis*. The Internet Journal of Infectious Diseases. 2012 Volume 10 Number 1.

Abstract

Background: Daptomycin has shown efficacy in patients with diabetes in skin and skin structure infections caused by Gram-positive pathogens. However, data are limited in patients with osteomyelitis. This study evaluated the safety and clinical response rate of patients treated with daptomycin for moderate to severe diabetic foot infections with osteomyelitis. **Methods:** This was a retrospective, multicenter study. Standardized case report forms were used to collect available data on each patient. A clinical response of; cure, improvement, failure, clinical relapse, or non-evaluable and microbiologic outcomes of; eradication, presumed eradication, persistence, or presumed persistence was determined by each investigator. Information on adverse events was collected throughout the entire study. **Results:** Twenty-one patients were identified from 2 clinics in the United States. Patients received a mean daptomycin dose of 6.1 ± 0.4 mg/kg (range, 5.7–7.2 mg/kg) administered every 24 hours. The mean length of outpatient therapy was 28.9 ± 15.3 days (range, 9 to 57 days). The clinical success rate was 81.0% (17/21) at the end of therapy, and the overall clinical success rate ≥ 10 months following daptomycin therapy was 71.4% (15/21). The adverse event rate requiring daptomycin discontinuation was 4.8%. Three patients experienced adverse events possibly related to daptomycin. Two patients had elevated creatine phosphokinase, 1 to 2 times the upper limit of normal, and one patient had elevated hepatic enzymes. **Conclusions:** In this study, successful outcomes in patients with moderate to severe diabetic foot infections caused by Gram-positive pathogens suggest that daptomycin has a role for treating these complex infections.

SOURCES OF SUPPORT

This study was sponsored by the Cubist Pharmaceuticals, Inc. Medical Affairs Department. The sponsor participated in the study design and statistical analyses of data.

DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

R.D.W. is an owner/stockholder in Pathogenius, LLC and a participant in the Cubist Speakers Bureau. M.G.C., E.H., M.Y., and H.L.H.-R. are employees and shareholders of Cubist Pharmaceuticals, Inc., who sponsored this study.

INTRODUCTION

Osteomyelitis is a complication in approximately 20% of diabetic foot infections, posing significant risk for limb loss when accompanied by neuropathy and vascular disease.¹ The morbidity and related healthcare costs are high. In addition, there is an increased risk of mortality following amputations.² Treatment of osteomyelitis in these patients

often requires longer term antimicrobial therapy along with aggressive wound management.

Gram-positive pathogens, predominately *Staphylococcus aureus*, are the most common pathogens in diabetic foot infections.³ However, these infections often may be polymicrobial, involving Gram-negative aerobes and anaerobic pathogens.⁴ Due to the rising prevalence of methicillin-resistant *S. aureus* (MRSA) in patients with diabetic foot infections, anti-MRSA agents play an important role in management of these infections.³

Daptomycin is a cyclic lipopeptide antimicrobial that is active against Gram-positive bacteria, including MRSA. Daptomycin binds to bacterial cell membranes in a calcium-dependent manner and causes a rapid depolarization of membrane potential and consequent bacterial cell death. Daptomycin has been studied extensively in the treatment of complicated skin and skin structure infections and is FDA-

approved at a dose of 4 mg/kg daily. Daptomycin is also approved at a dose of 6 mg/kg for treatment of Gram-positive bacteremia, including right-sided endocarditis.

While limited data are available on the use of daptomycin for diabetic foot infections without osteomyelitis and in non-diabetic patients with osteomyelitis, data in diabetic patients with osteomyelitis are scarce.⁵⁻⁸ Daptomycin's in vitro bactericidal activity against resistant Gram-positive organisms (including MRSA)⁹⁻¹², good tissue penetration in diabetic patients,^{13,14} once-daily dosing, and long-term safety data¹⁵ warrant its investigation for the treatment of patients with diabetic foot osteomyelitis.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

This was a retrospective study of patients with moderate to severe diabetic foot infections, according to Infectious Disease Society of America classification,⁴ with underlying osteomyelitis caused by a Gram-positive pathogen who were treated with daptomycin in two institutions from January 2005 to October 2009. One site was a wound care center with one physician that treated patients predominantly in the outpatient setting. The second center was an infectious diseases clinic supported by two infectious diseases physicians that were the lead participants in the hospital wound clinic. Both centers served a large, predominantly rural geographic region. Typical patients treated at both centers were diabetic, hypertensive, obese, and had poor vascular supply. Patients who met the inclusion criteria were identified and enrolled in the study consecutively.

PATIENT INCLUSION CRITERIA

Subjects 18 years or older with type 1 or 2 diabetes mellitus, as defined by the American Diabetes Association guidelines,¹⁶ were included. A diagnosis of moderate to severe foot ulcer and osteomyelitis, according to the Infectious Disease Society of America guidelines,⁴ and confirmation of osteomyelitis by x-ray and/or bone biopsy were required. Infection caused by a Gram-positive organism, confirmed by deep wound culture and/or bone biopsy, was also required, and patients had to have received at least 7 days of 6 mg/kg daptomycin and standard wound care at each center. Standard wound care included clinic visits 1-2 times weekly with debridement of the wounds performed 1-2 times weekly as clinically indicated. Repeat cultures were obtained when clinically indicated. All patients received pressure relief and topical wound care and dressings designed to promote healing and minimize

bacterial growth.

Additionally, 3 of the following signs and symptoms had to be documented at the initial baseline visit: wound discharge (exudate); erythema extending >1 cm from the wound edge; fluctuance; pain or tenderness to palpation; elevated total peripheral white blood cell (WBC) count >12,000/mm³ or >10% immature neutrophils (bands) regardless of total peripheral WBC count; or fever (defined by >37.5°C (axillary), >38°C (orally), 38.5°C (tympanically), or >39°C (rectally)).

PATIENT EXCLUSION CRITERIA

Patients were excluded from data collection if the infection was associated with a burn wound or uncomplicated skin or skin structure infection, including folliculitis and furunculosis, carbunculosis, and simple abscesses or superficial cellulitis. Patients were also excluded if they had received daptomycin as part of a controlled clinical trial (excluding the Cubicin Outcomes Registry & Experience [CORE[®]] program); had concomitant bacteremia, endocarditis, necrotizing fasciitis, or prosthetic material at the site of infection; or if they received immunosuppressive therapy with the exception of prednisone <5 mg/day.

DATA

Data were collected, when available, retrospectively from patient charts on all consecutive subjects in a standardized case report form designed for this study. At baseline, demographic data collected included age, gender, race, and ethnicity. A history of dialysis was recorded, and classification of the diabetic foot infection was made according to Infectious Diseases Society of America guidelines.⁴ Clinical aspects of diabetic foot infection, including wound discharge (exudate), erythema, local edema, and transcortical sinus tract (tunneling), were classified as mild, moderate, or severe. Also noted were underlying disease states, including peripheral neuropathy, hypertension, presence of foreign hardware, renal failure, congestive heart failure, history of prosthetic heart valve, cardiac disease, HIV/AIDS, peripheral vascular disease, or any other underlying disease the investigator felt was important. The investigator's primary diagnosis was recorded, including site on foot, number of ulcers, and type of radiology test done for osteomyelitis diagnosis. History of prior infections at that site; nutrition status; HbA1c; diabetes control at the time of infection; laboratory values, including serum creatinine, serum creatine phosphokinase, and prior hospitalization were noted. Data on wound size, topical

agents used, culture results with antibiotic susceptibility profiles, prior antibiotics (within 1 month of diagnosis), and concomitant medications including statin therapy were collected. Surgical intervention history, including mechanical and surgical debridement as related to the current infection, was documented.

During the daptomycin treatment period, all daptomycin dosage changes, dates of changes, and reasons for the changes were recorded, and concomitant antibiotics, topical agents, new radiology tests, and culture results with susceptibility testing were noted. Wound size, surgical interventions, wound assessments, and clinical signs and symptoms were recorded weekly when available.

Data collected at the end of daptomycin therapy, included additional continued antibiotics, topical agents, new radiology tests, culture results with susceptibility testing, wound size, surgical interventions, wound assessments, and clinical signs and symptoms. Additionally, the investigators recorded the assessment of clinical and microbiological response using definitions explained below.

At each of the follow-up periods, 5 to 7 months and ≥ 10 months after the end of daptomycin therapy, clinical assessment, antibiotic and topical agent use, culture and susceptibility data, and radiologic testing for osteomyelitis were recorded. Serum creatinine, creatine phosphokinase, hospitalization status, need for amputation, and adverse events for the entire study period were documented. The investigators also made a clinical and microbiologic assessment at each follow-up period.

OUTCOME ASSESSMENT DEFINITIONS

A clinical response classified as cure, improvement, failure, clinical relapse, or non-evaluable was determined by each investigator at the end of daptomycin therapy and at each of the 2 follow-up assessments. Outcome assessment definitions are explained in Table 1. Subjects whose clinical response was considered a cure or improvement at the end of therapy were evaluated for possible relapse at 2 follow-up visits, 5 to 7 months and ≥ 10 months after the end of daptomycin therapy. The clinical response at each follow-up visit was not collected for patients who failed therapy prior to the follow-up visit, discontinued daptomycin therapy due to lack of efficacy or adverse event, or were non-evaluable at the end of therapy. Non-evaluable patients were considered failures when calculating overall therapeutic outcome at end of therapy.

MICROBIOLOGIC OUTCOME DEFINITIONS

A bacteriological response of eradication, presumed eradication, persistence, or presumed persistence was determined by the investigator based on culture results at the end of daptomycin therapy and at each of the 2 follow-up assessment periods. Microbiologic outcome definitions are explained in Table 2.

DATA ANALYSIS

There was no hypothesis testing, and statistical analysis was limited to descriptive methods. Descriptive statistics, including mean, median standard deviation, minimum, and maximum, were reported with continuous data. Percentages were determined for categorical data. In addition to the determination of clinical outcome, the number of weeks to healing time was calculated and summarized. Among patients who failed treatment, the number of patients who required an amputation was recorded.

RESULTS

BASELINE PATIENT DEMOGRAPHICS AND CHARACTERISTICS

Twenty-one patients with at least one Gram-positive pathogen treated with daptomycin for diabetic foot infection with osteomyelitis were identified. In all cases bone was visible for the diagnosis of osteomyelitis in addition to radiologic tests when available. Patient baseline demographics and characteristics are summarized in Table 3.

Baseline microbiology is summarized in Table 4. In 76% (16/21) of patients, only 1 Gram-positive pathogen was identified from a bone or deep tissue culture at baseline, whereas 24% (5/21) had 2 isolates recovered. The most common baseline organism was *S. aureus*, which was present in 62% (13/21) of patients. Among 5 patients with 2 positive bone or deep tissue cultures at baseline, 2 patients had a Gram-negative pathogen with *S. aureus*. The other 3 patients had combinations of 2 Gram-positive pathogens. No other antibiotics were used in addition to daptomycin in these 5 patients. The Gram-negative infections were treated using topical anti-biofilm agents that were the standard of care for that site. Two patients infected with MRSA and other gram-positive pathogens relapsed by the first follow-up visit. The other 3 patients with 2 baseline positive cultures had successful outcomes.

Of the 5 patients that had MRSA as a baseline pathogen 3 had successful outcomes. Both failures were initially treatment successes at the end of therapy and then relapsed

at follow-up visits. Both failures also had other gram-positive pathogens at baseline, *Enterococcus faecalis* and *Staphylococcus aureus* group streptococcus in addition to MRSA. Additionally, 1 of these patients also had yeast isolated from the wound during therapy and both patients relapsed with polymicrobial infections.

Baseline disease state information is summarized in Table 4. The most common underlying diseases were hypertension, cardiac disease, and peripheral neuropathy. Peripheral vascular disease was recorded in 6 patients and was present in 3 out of 4 failures/relapses. One patient at baseline was receiving hemodialysis. Fifty-two percent (11/21) had prior history of infection at the same site, and 90% (19/21) had received debridement (surgical or mechanical) 30 days prior to starting daptomycin therapy. There was more than 1 ulcer at baseline on the same foot as the primary ulcer in 66.6% (14/21) of patients. Among these patients, there were a mean 3.1 ± 2.0 (range, 2-9) additional ulcers on the same foot as the primary ulcer. All infections were categorized as moderate osteomyelitis according to the Infectious Diseases Society of America guidelines.⁴

DAPTOMYCIN DOSE AND SITE OF ADMINISTRATION

The mean daptomycin dose patients received was 6.1 ± 0.4 mg/kg (range, 5.7-7.2 mg/kg). All patients were administered daptomycin every 24 hours and received daptomycin therapy in the outpatient setting. Two also received initial inpatient therapy for 6 and 31 days. The mean length of outpatient therapy was 28.9 ± 15.3 days (range, 9-57 days).

NON-STUDY ANTIBIOTICS

Eleven of 21 patients received antibiotics within 30 days prior to starting daptomycin. Most received a single drug, with ertapenem being the most common choice. Four patients received ≥ 2 drugs prior to daptomycin. Other previous antibiotics included gentamicin, imipenem, piperacillin/tazobactam, doxycycline, cephalosporins, or quinolones. Only 2 patients had prior vancomycin for 2 to 3 days. No prior antibiotics were administered in 7 patients, and previous antibiotics were unknown in 3 of the patients.

No concomitant antibiotics were administered with daptomycin in 16/21 patients. Five patients received >2 days of other antibiotics with daptomycin, including imipenem, ciprofloxacin, doxycycline and piperacillin/tazobactam.

Antibiotics were administered to 11/21 patients following the completion of daptomycin therapy. Of those patients, 2

were considered daptomycin failures, and doxycycline and tigecycline were subsequently used. Additionally, 2 patients received imipenem and cefepime for the treatment of Gram-negative pathogens identified from deep tissue cultures in the wound and were considered non-evaluable. The remaining 7 patients were switched to oral therapy (doxycycline, linezolid, or trimethoprim/sulfamethoxazole) to complete antibiotic therapy following daptomycin.

NON-ANTIBIOTIC MEDICATIONS

The most common non-antibiotic medications administered with daptomycin included drugs for the treatment of diabetes mellitus, such as insulin, glyburide, and metformin. Previous statin therapy was reported in 11/21 patients. It was unknown in one patient if statin therapy was stopped with the initiation of daptomycin, but the statins were not discontinued in the remaining patients. Previous statin therapy was unknown in 3 patients.

SURGICAL INTERVENTIONS AND ADJUNCTIVE THERAPY DURING TREATMENT

Surgical interventions were similar at both sites. Patients had an average of 3.1 ± 2.9 (range, 0-10) surgical debridements during daptomycin therapy. Only one visit per week was captured on the data collection form, so more frequent debridements were not recorded. More interventions categorized as "other" were documented for one site with a mean of 10.9 ± 5.7 interventions compared with 3.9 ± 3.8 for the other site. The most common "other" intervention at the first site included hyperbaric oxygen at most visits in all patients, and a wound vacuum was used in 6/7 patients. Those interventions were not reported at the other site.

Topical agents were used in addition to daptomycin therapy in several patients. Eighty-one percent (17/21) of patients received topical agents at baseline, and 95% (20/21) received topical agents at some point during the daptomycin treatment period. The most common topical agents varied between the 2 sites. The most common agents used at one site included lactoferrin, xylitol, and iodisorb gel, whereas the most common topical agents used at the other site were Dakin's solution, calcium alginate, promogran, and mesalt.

CLINICAL AND MICROBIOLOGICAL OUTCOME

Clinical and microbiologic outcomes at the end of daptomycin therapy are summarized in Table 5.

At the end of therapy, a successful clinical outcome was reported for 17/21 patients, and a successful microbiologic response was observed in 16/21 patients. One patient was

missing the end of therapy microbiologic assessment but had presumed eradication and a clinical response of cure at the follow-up visits. Two patients were failures at the end of daptomycin therapy. An additional 2 patients were non-evaluable at the end of therapy due to need for additional antibiotic therapy for Gram-negative pathogens and presumed persistence of the Gram-positive isolates (microbiologic failure). These patients were considered treatment failures in the analysis set. At the first follow-up visit, 2 additional patients relapsed and were considered failures, resulting in an overall success rate of 71.4% (15/21). Of the 4 patients who failed daptomycin therapy initially or relapsed at the follow-up visit, 3 had peripheral vascular disease. Additionally, 2 of the 4 patients were infected with MRSA at baseline.

Of the 2 patients that were determined a failure at the end of daptomycin therapy both received amputations. One patient had an 18-year history of previous gas gangrene, a flap closure, and chronic osteomyelitis. The patient refused amputation until all other non-surgical options had been exhausted. The patient failed multiple different courses of antibiotics, including one with daptomycin, and eventually required a below the knee amputation. The other patient that was a failure had chronic Charcot foot that failed reconstruction in part due to severe PVD and had a history of chronic osteomyelitis in that foot. Ultimately the wound broke down and required a Syme’s amputation.

Both patients that relapsed following daptomycin therapy had microbiologic cures of the infection from the baseline pathogen when treated with daptomycin. However, both patients later relapsed with different pathogens and required subsequent amputation. One patient had a crush injury leading to severe vascular disease, and the other patient had a history of a non-healing wound which was considered the reason for amputation.

SAFETY PROFILE

Table 6 summarizes the adverse events recorded during this study. Seven patients had at least 1 adverse event during the study period, and 1 serious adverse event was documented. Three of the adverse events were possibly related to daptomycin, 2 patients had increased creatine phosphokinase and one had increased hepatic enzymes. Both patients with creatine phosphokinase elevations were also on concomitant statin therapy, and the creatine phosphokinase increased to 1 to 2 times the upper limit of normal for blood creatine phosphokinase. No patients had a creatine phosphokinase

elevation >5 times the upper limit of normal. One unrelated serious adverse event, activation of Ménière’s disease, was reported.

Daptomycin was discontinued in one patient due to the increased creatine phosphokinase that occurred on day 15 and was considered a daptomycin failure. The other patient experienced a creatine phosphokinase elevation on day 18 of daptomycin therapy which subsequently resolved and was successfully treated for 40 days with 7.1 mg/kg daily of daptomycin. One other patient had an adverse event unrelated to daptomycin which resulted from the peripherally inserted central catheter (PICC) line falling out on day 56 of daptomycin therapy. The patient was changed to oral therapy with doxycycline. Subsequently, that patient was a clinical relapse at the first follow-up visit.

Figure 1

Table 1: Outcome Assessment Definitions

Clinical Response	Definition
<i>Cure</i>	A resolution of clinical signs and symptoms with no need for additional antibiotic therapy or cleared infection with a negative culture reported at the end of daptomycin therapy.
<i>Improvement</i>	A partial resolution of clinical signs and symptoms, with or without the need for additional antibiotic therapy at the end of daptomycin therapy. Patients designated as cured or improved could also have received step-down therapy with oral antibiotics that had activity against the Gram-positive organism causing the infection.
<i>Failure</i>	An inadequate clinical response to daptomycin therapy, culture results suggestive of persistent pathogen, development of resistant organism while on therapy, discontinuation of daptomycin for an adverse event, or worsening or new/recurrent signs and symptoms necessitating the need for a change in antibiotic.
<i>Clinical Relapse</i>	Patients who had been categorized as cured or improved but who, at the follow-up visits, displayed recurrence of signs and symptoms of infection after the initial response.
<i>Non-evaluable</i>	If investigators were unable to determine response at the end of daptomycin therapy because the patient record did not contain the information appropriate to determine <i>cure</i> , <i>improvement</i> , or <i>failure</i> .

Figure 2

Table 2: Microbiologic Outcome Definitions

Microbiologic outcome	Definition
<i>Eradication</i>	The baseline causative pathogen was not isolated from the same site at the end of daptomycin therapy.
<i>Presumed eradication</i>	No culture data was available and the patient's clinical response was classified as <i>cure</i> or <i>improvement</i> at the end of daptomycin therapy.
<i>Persistence</i>	The baseline causative pathogen was isolated from the same site at the end of daptomycin therapy.
<i>Presumed persistence</i>	No culture data was available and the patient's clinical response was classified as <i>failure</i> at the end of daptomycin therapy.
<i>Recurrence</i>	Isolation from the original site of infection showed at least one of the original Gram-positive pathogens that had been previously eradicated.

Figure 3

Table 3: Baseline Demographics

Total number enrolled, N=21	
Age(yr)	
Mean ± SD	55.8 ± 13.9
Range	22–82
Gender	
Male, n (%)	13 (61.9)
Female, n (%)	8 (38.1)
Race	
Black or African American, n (%)	1 (4.8)
White, n (%)	20 (95.2)
Weight (kg)	
Mean *	92.8 ± 19.3
Range	63.7–139
Infection location on foot	
Non-plantar, n (%)	8 (38.1)
Plantar, n (%)	7 (33.3)
Missing, n (%)	6 (28.6)
Diagnosis based on:	
Bone biopsy, n (%)	16 (76.2)
Radiology, n (%)	5 (23.8)

Figure 4

Table 4: Baseline Microbiology and Underlying Disease States

Total number enrolled, N=21	
Microbiology at baseline ^a , n	
<i>Staphylococcus aureus</i>	13
MRSA	5
MSSA	7
<i>S. aureus</i> , unknown	1
<i>Enterococcus</i> species	4
<i>E. faecium</i> , vancomycin-resistant	1
<i>E. faecalis</i> , non vancomycin-resistant	3
Coagulase-negative <i>Staphylococcus</i>	3
<i>Streptococcus</i> species	4
Group B <i>Streptococcus</i>	3
Other <i>Streptococcus</i>	1
Other pathogens	3
Gram-negative organism	2
Other Gram-positive organism	1
Subjects with an underlying disease at baseline ^b , n (%)	
Hypertension	14 (66.7)
Cardiac disease	13 (61.9)
Peripheral neuropathy	10 (47.6)
Peripheral vascular disease	6 (28.6)
Congestive heart failure	3 (14.3)
Renal failure	2 (9.5)
Other	9 (42.9)
History of infection at baseline, n (%)	
Prior infection at the same site	11 (52.4)
Prolonged hospitalization within 6 months	2 (9.5)
Malnourished	1 (4.8)
Diabetes controlled (investigator assessed)	7 (33.3)
More than one ulcer site on the same foot	14 (66.7)
Number of ulcer sites on the same foot, n=14	
Mean	3.1 ± 2.0
Range	2–9

^aSubjects may have had multiple pathogens; 27 isolates were recovered in 21 patients.

^bSubjects may have had more than one disease and is listed if recorded in the patient's chart

Figure 5

Table 5: Clinical Outcome at End of Daptomycin Therapy

Clinical Response, n (%)	
Cure	5 (23.8)
Improved	12 (57.1)
Failure	2 (9.5)
Non-evaluable	2 (9.5)
Clinical success	17/21 (81.0)
Microbiological response	
Eradication	1 (4.8)
Presumed eradication	15 (71.4)
Persistence	1 (4.8)
Presumed persistence	3 (14.3)
Missing response	1 (4.8)
Microbiological success	16/21 (76.2)
Overall therapeutic outcome	
Success	16/21 (76.2)
Failure	5/21 (23.8)

Figure 6

Table 6: Summary of Most Common Treatment-Emergent Adverse Events

Subjects with treatment-emergent adverse event, n (%)	
Gastrointestinal disorders, n (%)	5 (23.8)
Administration site, n (%)	4 (19.0)
Catheter-related complication	2 (9.5)
Catheter site hemorrhage	2 (9.5)
Wound and procedural complications, n (%)	4 (19.0)
Laboratory abnormalities, n (%)	5 (23.8)
Blood creatine phosphokinase increased	2 (9.5)
Blood glucose increased	2 (9.5)
Blood potassium increased	2 (9.5)
Hemoglobin decreased	2 (9.5)

DISCUSSION

This retrospective study provides information about patients with moderate to severe diabetic foot infections with osteomyelitis that received daptomycin therapy for Gram-positive infections from 2005 to 2009. The results of this analysis suggest that daptomycin is efficacious in the treatment of diabetic foot infections with osteomyelitis caused by Gram-positive organisms, including MRSA.

Currently there are limited data on the use of daptomycin for the treatment of diabetic foot infections with osteomyelitis. An in vivo microdialysis method was used to measure tissue concentration in diabetic and healthy patients.¹³ The degree of tissue penetration, defined as the ratio of the area under the free drug concentration time curve for tissue to that for plasma, was 0.93 ± 0.61 for diabetic subjects and 0.74 ± 0.09 for healthy subjects. Another study used similar methodology and evaluated daptomycin concentrations in healthy tissue, inflamed subcutaneous adipose tissue, and the bones of diabetic patients with bacterial foot infections.¹⁴ The mean ratios of the free drug concentration time curve for tissue to that for plasma was 1.44, 0.98, and 1.08 in healthy tissue, inflamed subcutaneous adipose tissue, and bones, respectively. These studies demonstrate that daptomycin effectively penetrates the bone and tissue in diabetic patients.

Additionally, a post hoc analysis of data from 2 large, Phase III, prospective clinical trials of daptomycin for the treatment of cSSSI demonstrated similar success rates between treatment groups in a subset of diabetic patients

with foot infections.^{17,18} Similar outcomes were observed in a post-hoc analysis of data from patients with complicated *S. aureus* bacteremia with osteoarticular infections in a Phase III, open-labeled, prospective study.^{15,19}

In this study, daptomycin demonstrated a favorable safety and tolerability profile with relatively low clinical failure rates. At the end of therapy a successful outcome was reported in 81% (17/21) of patients, with a successful microbiologic response reported in 76% (16/21) of patients. Two patients were reported as failures, and 2 patients were considered non-evaluable at the end of daptomycin therapy due to concomitant Gram-negative infections. An additional patient was considered a microbiologic failure because of a missing microbiologic assessment at the end of therapy. However, that patient had an improved clinical response at the end of therapy and was considered a cure with presumed microbiologic eradication at the second follow-up visit.

Wound management in this study was similar between the 2 sites, with the exception of topical agents used and that hyperbaric oxygen and wound vacs were used only at one site. One center used topicals that were anti-biofilm agents in contrast to the other site, which used agents that were antibacterials. The anti-biofilm agents specifically diminish colony defenses of the biofilm, block bacterial attachment, and disrupt the polymeric matrix of the biofilm. The anti-biofilm topical agents were used in conjunction with debridement, a method that has been shown to make the bacteria more susceptible to antibiotics.²⁰

Treating diabetic patients with foot osteomyelitis is complex and depends not only on the antimicrobial agent used but also a variety of host factors, such as vascular performance, boney perfusion, sequestrum, extent of surgical debridement, glycemic control, and factors related to ulcer causation. These host factors interplay with microbiological cure rates and ulcer cure rates, and it is believed that a combination of improvement of the host factors and antimicrobial therapy is necessary for successful outcomes in patients with diabetes mellitus and osteomyelitis foot infections.

This study had several limitations due to the retrospective, non-comparative, non-blinded, and non-randomized study design. Data collected was limited to that recorded in the patient chart. Due to changes in microbiology and wound care management during the study period and the complexity of these patients no comparator was evaluated. There was no differentiation made between chronic and acute

osteomyelitis. There also exists a large variation in the management of wound care; therefore, the generalisability of this study is limited by wound care management. In addition, the small sample size makes it difficult to draw strong conclusions applicable to other dissimilar populations.

Patients with diabetic foot infections and osteomyelitis pose difficult clinical challenges, including impaired wound healing resulting from comorbidities such as peripheral neuropathy and peripheral vascular disease. Furthermore, these patients typically have multiple ulcers on the same foot and a history of prior infection at the same site. Despite these challenges, this study of patients with moderate to severe diabetic foot infections had an overall 71.4% (15/21) success rate at the follow-up visit ≥ 10 months after daptomycin therapy. All of the patients received antibiotic therapy in the outpatient setting, which was possible given daptomycin's once-daily dosing regimen. In summary, the results of this study suggest that daptomycin has a role in the treatment of diabetic foot infections with osteomyelitis and warrants further investigation.

ACKNOWLEDGMENTS

Patient case report forms were completed by investigators at each site, and inVentiv Clinical Solutions, LLC. (Hunt Valley, MD) verified the data.

The authors thank Lisa Morrow of Southwest Regional Wound Care Center (Lubbock, TX) and Denise Walter of Regional Infectious Diseases & Infusion Center, Inc. (Lima, OH) for countless hours of data collection. We also thank Meng-Yun Maureen Lin for her statistical contributions to this study. Mary-Ellen Marx and Diana Talag of PharmaWrite copyedited and formatted the final version of the manuscript. This service was funded by Cubist.

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